REMARKS/ARGUMENTS

Claims 1-4, 6, 8-17, 19-21, and 23-24 are pending in this application and presented for examination. Claims 1, 3, 4, 16, 19, 21 and 22-24 have been amended. Claims 5, 18 and 22 have been canceled without prejudice. Reconsideration is respectfully requested.

I. FORMALITIES

Claims 1, 3, 4, 16 and 21 have been amended to recite that the piperdinopyrimidine derivative is minoxidil or a pharmaceutically acceptable salt thereof. Support for the amendment is found, for example, in claims 5, 18 and 22, which claims have been canceled without prejudice. Claims 19, 23 and 24 have been amended to update their dependencies or to correct a minor typographical errors. Thus, no new matter has been introduced. As such, Applicants respectfully request that the amendments be entered.

II. THE INVENTION

The present invention provides *inter alia*, a homogeneous pharmaceutical composition for topical administration comprising: at least 5% by weight, based on the total weight of the composition, of minoxidil or a pharmaceutically acceptable salt thereof. Advantageously, the compositions of the present invention allow for increased percentage of minoxidil, but without the disadvantages associated with a high propylene glycol concentration. The composition can be formulated into a any suitable topical pharmaceutical preparation, which includes solutions, lotions, ointments such as lacquers, mousses, foams, sprays, aerosols, shampoos and/or conditioners, gels, creams, pastes, and other preparations known in the art. The composition may also include other ingredients such as preservatives, buffers, stabilizers, propellants and the like.

III. DOUBLE-PATENTING REJECTION

The Examiner has provisionally rejected claims 1-6, 8-9, and 12-19 as allegedly being obvious over the claims of co-pending U.S. Patent Application No.10/124,197 because of

obviousness-type double-patenting. As a Terminal Disclaimer has already been filed in U.S. Patent Application No.10/124,197, the double-patenting rejection in this application has been rendered moot. As such, Applicants respectfully request that the Examiner withdraw this double-patenting rejection.

IV. REJECTIONS UNDER 35 U.S.C. § 103(a)

A. Bazzano by itself, or optionally in view of WO 97/12602 (Weiner *et al.*)

The Examiner has rejected claims 1-3, 5-6, 8-9, 12-19 and 21-23 as allegedly being obvious over Bazzano by itself, or optionally in view of WO 97/12602 (Weiner *et al.*). In response, Applicants respectfully traverse the rejection.

In the Office Action, the Examiner states:[1]

> Bazzano teaches the use of pharmaceutically acceptable acid salt. See column 19, lines 1-25. Bazzano states that minoxidil or its derivatives and analogs that are described in US patents 5910928, 3637697, 3461461, 4139619, and 4596812 are incorporated into the reference. US patent 3,461,461 teaches the acid salt derivatives including lactic acid and other instantly claimed acids of minoxidil. Bazzano discloses that a major problem in influencing hair growth is obtaining good percutaneous absorption of the active compounds. The retinoid compounds cause excellent absorption of the hair follicles. See column 19, lines 35-40. The formulation can contain any pharmaceutically acceptable carrier, additive, or solubilizer.
>
> Although Bazzano states that a minoxidil derivative/analog many be utilized, Bazzano does not explicitly teach the use of an acid addition.
>
> WO teaches a topical composition for minoxidil. WO discloses that making materials more hydrophilic, improves penetration through the hair follicle. Minoxidil is modified by reacting it with an organic acid such as lactic acid. See page 4.
>
> It is deemed obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Bazzano and utilize [the] instant minoxidil acid salt. One would be motivated to do so since Bazzano teaches the suitability of minoxidil or its derivative

[1] Page 4 of the Office Action dated September 22, 2004.

> in the composition and Bazzano's teachings incorporate other US patents wherein the instant acid salt derivative is taught. Therefore, one could reasonably expect similar results with the use of a minoxidil acid salt derivative.
>
> Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made [to] look to the teachings of WO and be further motivated to utilize the instant acid derivative. **One would have been motivated to do so since both references teach that by adding salt to minoxidil, one obtains a more soluble form of the active.** [Emphasis added].

In constructing the alleged obviousness rejection, the Examiner has impermissibly used *additional references* such as the references "incorporated by reference" into Bazzano. Thus, the Examiner is relying on references not supported in the obviousness rejection. In this regard, the Examiner is respectfully directed to M.P.E.P. § 706.02(j) wherein it states:

> [w]here a reference is relied on to support a rejection, whether or not in a minor capacity, that reference should be positively included in the statement of the rejection. See *In re Hoch*, 428 F.2d 1341, 1342 n.3 166 USPQ 406, 407 n. 3 (CCPA 1970).

In this instance, the Examiner has impermissibly used references such as U.S. Patents Nos. 5,910,928, 3,637,697, 3,461,461, 4,139,619, and 4,596,812, which references are not even of record. Under M.P.E.P. §706.02(j), where a reference is relied on to support a rejection, *whether or not in a minor capacity*, that reference should be positively included in the statement of the rejection. For this reason alone, the Examiner is respectfully requested to withdraw the rejection as being improper. Moreover, Applicants have reviewed Bazzano (U.S. Patent No. 5,183,817) and fail to find support for the Examiner's assertion that "that by adding salt to minoxidil, one obtains a more soluble form of the active."

In any event, not withstanding the impropriety of the foregoing rejection, Bazzano teaches a minoxidil cream containing retinoic acid, minoxidil (0.5%-5%), ethanol, propylene glycol (5-50%), and distilled water (up to 10%). Bazzano further teaches the use of a pharmaceutically acceptable salt, which salt is not specified (*see*, col. 19, lns. 1-25). Bazzano also discloses that a major problem in influencing hair growth is obtaining good percutaneous

absorption of the active compounds, and that retinoid compounds cause excellent absorption by the hair follicles (*see*, col. 19, lns. 35-40). Bazzano teaches that an essential ingredient in the formulation is a retinoid. Bazzano teaches at column 5, lines 16-29, the following:

> The present invention combines the use of retinoid compounds with minoxidil, or its analogs or derivatives or minoxidil-type compounds (hereinafter collectively referred to simply as "minoxidil"). ***The stimulatory actions of both compounds can synergistically promote each others' effect. Retinoids can initiate cell growth and differentiation (not initiated by minoxidil), and minoxidil can promote the vasodilatory and mitogenic action not obtained with the retinoids.*** While neither compound alone may have profound effects on advanced alopecias, in combination the compounds are very effective as promoters of new hair growth in areas of alopecia. [Emphasis added].

From the foregoing, it is clear that Bazzano teaches that the combination of minoxidil and a retinoid is synergistic. Bazzano also points out at column 5, lines 30-41 the following:

> [t]he net result of application of minoxidil and retinoids is initiation and production of new hair growth and conversion of vellus to terminal hair growth, i.e., the increase in size from a vellus to a terminal hair and the continued and more prolonged maintenance of the hair in the anagen phase. ***As noted previously, this effect is obtained not merely as the addition of two compounds, but as synergism, i.e., the combination of these substances in the present invention produces an effect which cannot be produced by either compound separately under conditions of its use and, therefore, represents a major advance in the treatment of alopecia.***

As such, Bazzano teaches that minoxidil and the retinoid act synergistically and "[t]he combination of these substances in the present invention produces an effect which cannot be produced by either compound separately under conditions of its use and, therefore, represents a major advance in the treatment of alopecia." (Please see col. 5, line 37-41).

Thus, it is evident that the retinoid is an essential component to Bazzano. However, the present formulation does not require a retinoid. In view of Bazzano, a skilled person would not have been motivated to prepare a formulation without the requisite retinoid, as Bazzano teaches that the retinoid is an essential feature.

Applicants assert that the present invention is unobvious over Bazzano. Bazzano emphasizes the importance of a retinoid, however, Applicants' formulation does not contain such a component. Therefore, a skilled artisan would have no expectation of success that the formulation as presently claimed would be effective, without the presence of a retinoid.

The Examiner states that the current claim language does not specifically exclude other ingredients such as retinoic acid. However, the Examiner is respectfully reminded that the foregoing is **not the test for obviousness**. The test is whether the prior art reference or combination of references teach or suggest all the limitations of the claims.

Weiner *et al.* do not supply the deficiencies of Bazzano: Weiner *et al.* teach that minoxidil can be modified to make it more hydrophilic. For example, it may be converted to an acid such as a lactic acid salt, or by encapsulating it in cyclodextrin[2]. However, a fair reading of Weiner *et al.* would **require** that *after* the minoxidil has been made more hydrophilic, it must be encapsulated. That is, **[t]he modified therapeutic material is encapsulated in a lipid vesicle** and the lipid vesicle is delivered to the skin portion having hair follicles, whereby the hair follicles appear to act as a conduit for the therapeutic material. [Emphasis added] (Please see page 3, lines 7-10).

Thus, the combination of teachings of Bazzano and Weiner *et al.* would produce an encapsulated composition of minoxidil and retinoic acid, wherein the minoxidil was previously made more hydrophilic by either treating with an organic acid, or wherein the minoxidil is encapsulated in cyclodextrin. In no instance would the hypothetical combination produce the claimed invention. As such, Applicants respectfully request that the Examiner withdraw the rejection.

B. WO 95/25500 (Navarro *et al.*) in view of WO 97/12602 (Weiner *et al.*)

The Examiner has rejected claims 1-4, 5-6, 8-9, 12-19 and 21-23 as allegedly being obvious over WO 95/25500 (Navarro *et al.*) in view of WO 97/12602 (Weiner *et al.*).

1. Navarro

Essentially, Navarro teaches encapsulating minoxidil in a cyclodextrin carrier. The role of cyclodextrin in Navarro is to function as a "host" molecule to trap the minoxidil "guest" molecule inside the ring. In addition, Navarro teaches that the prior art use of propylene glycol is to solubilize the active ingredient and to ensure good penetration. Navarro further teaches the problem of using propylene glycol, which tends to give a greasy, shiny and unattractive appearance to the hair upon application. In solving these prior art deficiencies, Navarro teaches the use of γ-cyclodextrin in order to assist in solubilization and ensure good penetration of minoxidil while avoiding high amounts of propylene glycol. It is this minoxidil-cyclodextrin "host-guest" complex that imparts improved solubility properties and ensures good penetration of the Navarro's formulation.

2. Weiner *et al.*

The Examiner combines the teaching of the encapsulated compounds of Navarro with the teaching of Weiner *et al.* Weiner *et al.* teach the use of liposomes to encapsulate minoxidil and make it more deliverable.

Weiner *et al.* actually teach that the encapsulation process comprises two steps. In the first step, "the modification step," Weiner *et al.* teach, "**[f]irst, the materials themselves are modified to make them more hydrophilic by reacting them with an acid or base, e.g., an organic acid or base such as lactic acid**. In fact, the use of hydrophobic materials in lipid vesicles is contraindicated since they do not penetrate as well as the hydrophilic materials." [Emphasis added]. (Please see, page 4, lines 13-18). Thus, the "modification step" is to make minoxidil more hydrophilic.

In the second step, the material so modified is then encapsulated. Weiner *et al.* teach, **[t]he modified therapeutic material is encapsulated in a lipid vesicle** and the lipid

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[2] Although Weiner states that the salt could be made by reacting the therapeutic material with a dextrin such as cyclodextrin, it **must** mean encapsulation since cyclodextrin is not ionizable.

vesicle is delivered to the skin portion having hair follicles, whereby the hair follicles appear to act as a conduit for the therapeutic material. [Emphasis added] (Please see page 3, lines 7-10).

With regard to step 1, "the modification step," Weiner *et al.* teach that minoxidil can be modified to make it more hydrophilic. For example, it may be converted to an acid such as a lactic acid salt or by encapsulating it in cyclodextrin. However, Weiner *et al.* **requires** that *after* the first step is accomplished, the second step must still be undertaken. That is, **[t]he modified therapeutic material is encapsulated in a lipid vesicle** and the lipid vesicle is delivered to the skin portion having hair follicles, whereby the hair follicles appear to act as a conduit for the therapeutic material. [Emphasis added] (Please see page 3, lines 7-10).

3. The prior art references teach encapsulated minoxidil

Thus, a fair reading of both references is that in order to make minoxidil more deliverable, it **must be** encapsulated either by cyclodextrin as taught by Navarro or a non-phospholipid lipid vesicles, *i.e.*, a liposome as taught by Weiner *et al.* With regard to Navarro, the procedure is to encapsulate "unmodified" minoxidil in a cyclodextrin, preferably a γ-cyclodextrin. With regard to Weiner *et al.*, the procedure is to first modify minoxidil and thereafter encapsulate the modified minoxidil in a liposome. Neither Navarro nor Weiner teach or suggest that unencapsulated minoxidil can be delivered effectively in a polar solvent. In this regard, Applicants respectfully direct the Examiner's attention to Wiener *et al.* at page 6, Table 1, wherein the penetration capabilities of Formulation III (formulation of lactic acid salt of minoxidil encapsulated in a liposome) against Formulation XI (formulation unencapsulated lactic acid salt of minoxidil) are set forth. The results indicate that the encapsulated lactic acid salt of minoxidil has significantly greater penetration capabilities over the unencapsulated formulation. Thus, there is no motivation to react minoxidil with an acid, without encapsulating the resulting minoxidil salt in a liposome of Weiner *et al.*

4. The Examiner was unconvinced that the declaratory evidence was sufficient to remove a similar rejection.

The Examiner stated in the Office Action:

> Weiner teaches that a number of different modifications may be made to the minoxidil. One such modification is provided by reacting minoxidil with an organic acid such as lactic acid. The minoxidil may also by converted to a salt by reacting it with a cyclodextrin. See page 3. **Weiner states that the use of a minoxidil acid salt addition provides substantial penetration and cyclodextrin salt addition is the "next best".** See page 7. (Emphasis added, page 7 of the Office Action dated September 22, 2004).

Further, the Examiner states that it would have been obvious:

> ..at the time the invention was made to combine the teachings of Navarro et al. and Weiner et al. and substitute Navarro's cyclodextrin with the instant acid to convert minoxidil into a salt. One would be motivated to do so since Weiner teaches that by converting the minoxidil to a hydrophilic compound, it penetrates the skin penetrate [sic]. More specifically, Weiner teaches the conversion of minoxidil into a salt form by reacting it with an organic acid such as instant lactic acid or with cyclodextrin and notes that although both provide penetration of minoxidil, the acid salt addition has a better effect than the cyclodextrin salt addition. Therefore, one would have been motivated to use an acid salt addition to convert minoxidil into a hydrophilic compound rather than Navarro's cyclodextrin since **Weiner teaches the acid salt addition has better penetration into the skin**. (Emphasis added, Page 7)

The Examiner apparently is stating that Weiner teaches the interchangeability of "minoxidil lactic acid salt" (of Weiner) with the "cyclodextrin encapsulated minoxidil" (of Navarro) and so a skilled person would substitute the lactic acid salt of Weiner into the teaching of Navarro. From the Examiner's point of view, this combination would render the parent invention obvious. Applicants respectfully disagree.

5. Applicants traverse such a rejection

As discussed above, Weiner *et al.* teach that the formulation disclosed therein is a two step process. Any teaching of interchangeability of "minoxidil lactic acid salt" and

"cyclodextrin encapsulated minoxidil" is done within the first modification step. Weiner *et al.* then teach that the so modified minoxidil be encapsulated within a lipid vesicle to effectuate being delivered to the skin portion having hair follicles, whereby the hair follicles appear to act as a conduit for the therapeutic material.

When the Examiner states, "**Weiner states that the use of a minoxidil acid salt addition provides substantial penetration and cyclodextrin salt addition is the "next best"** and "**Weiner teaches the acid salt addition has better penetration into the skin,**" these results are *after* Weiner *et al.* encapsulates the modified minoxidil into a liposome. Weiner *et al.*, states[3]:

> As can be seen from the data shown on this table, **Formula III, the glycerol dilaurate/lactic acid vesicles had twice the penetration into the deepest skin strata of any other formulation. The next best were the commercial Rogaine® preparation and the preparation having the cyclodextrin salt and ethanol oxide.**

The best is "**liposomal encapsulated** lactate acid minoxidil" (Formula III)[4]. The "next best," was "**liposomal encapsulated** cyclodextrin minoxidil" (Formula II)[5] and Rogaine (Formula XII). Thus, the Examiner's comments are clearly taken out of context. Weiner *et al.* teaches that the best formulation is "**liposomal encapsulated** lactate acid minoxidil". The "next best," was "**liposomal encapsulated** cyclodextrin minoxidil."[6]

Second, to interchange the "lactic acid salt of minoxidil" with the "γ-cyclodextrin encapsulated minoxidil" would destroy the aim of Navarro. The proposed modification that the Examiner contemplates of interchanging a "lactic acid salt of minoxidil" with "γ-cyclodextrin encapsulated minoxidil" would no longer follow the encapsulation teaching of Navarro.

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[3] Weiner et al., page 7, lines 11-15.
[4] 3rd row of Table 1 of Weiner et al., page 6.
[5] 2nd row of Table 1 of Weiner et al., page 6. In fact, Applicants are of the opinion that this formulation is in fact double encapsulated. It is first encapsulated within cyclodextrin and then into a liposome.
[6]The data presented in Example 3 of Weiner shows that minoxidil reacted with lactic acid, but not encapsulated in a lipid vesicle, is essentially undeliverable into hairless rat skin, whereas lipid vesicle encapsulated lactic acid-treated minoxidil penetrated living skin strata more deeply than the other tested formulations (please compare formulations III and XI in Table 1, on page 6 in the "Living Skin Strata" column and review the paragraph on page 7, lines 9-17

Under MPEP § 2143.01, in making a *prima facie* case of obviousness, the Examiner's proposed modification **cannot** render the prior art unsatisfactory for its intended purpose.

> MPEP § 2143.01:
>
> If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, **then there is no suggestion or motivation to make the proposed modification**.[Emphasis Added] *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

The Examiner's proposed modification would eviscerate Navarro's primary aims and render Navarro's invention unsatisfactory for its intended purpose. The hypothetical formulation would no longer contain a cyclodextrin encapsulated minoxidil molecule. In the absence of cyclodextrin, there would be insufficient penetration without the presence of high concentrations of propylene glycol, which tends to give a greasy, shiny and unattractive appearance to the hair. Thus, the Examiner's proposed modification would destroy Navarro's objective of producing a lotion which is pleasant to use by formulating minoxidil within an inclusion complex of cyclodextrin. Thus, this proposed modification would contain minoxidil, propylene glycol and ethanol, which would be the unpleasant product that Navarro is trying to avoid. In view of the foregoing, the withdrawal of the obviousness rejection is respectfully requested.

6. The present invention is patentable over the combination of Navarro and Weiner *et al.*

Again, the cyclodextrin of Navarro acts to "host" the hydrophobic free base of minoxidil, and thereby assists in solubilizing minoxidil in polar solvents consisting of one or more polyalcohols and water. However, once minoxidil is ionized to form a salt, such as in the presence of lactic acid, it is rendered a hydrophilic molecule, and no longer a candidate for being a hydrophobic "guest" for the "host" cyclodextrin molecule. The addition of Navarro's

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of Weiner). Based on this data, those of skill in the art certainly would have no motivation to react minoxidil with an acid, but not encapsulate the minoxidil salt in a lipid vesicle.

cyclodextrin to the formulation of the present invention would render useless the invention of Navarro, as the primary purpose of cyclodextrin is no longer relevant. That is, once minoxidil is a hydrophilic salt, it is no longer suitable for inclusion in the hydrophobic interior of cyclodextrin.

Moreover, the addition of the liposomes of Weiner *et al.* provide absolutely no advantage to the present invention as the present invention has already achieved sufficient solubility of minoxidil as well as excellent penetration into the skin. Thus, Applicants maintain that the present claims are patentable in view of the Navarro and Weiner *et al.*

C. Bazzano in view of WO 97/12602, and further in view of Uchikawa *et al.*

The Examiner has rejected claims 10-11, 20 and 24 as being allegedly obvious over Bazzano in view of WO 97/12602, and further in view of Uchikawa *et al.* In response, Applicants respectfully traverse the rejection.

The Examiner states:[7]

> It would have been obvious at the time the invention was made to combine the teachings of Bazzano, WO, and Uchikawa and utilize benzyl alcohol in the solvent system. One would have been motivated to do so since Uchikawa et al teach the use of either ethanol or benzyl alcohol as functional equivalents, i.e. solvents, in the hair tonic. Therefore, it is prima facie obvious to substitute one equivalent solvent for another, i.e. Bazzano's ethanol with instant benzyl alcohol, since the prior art establishes that both are functionally equivalent and are utilized for the same purpose.

The Examiner is relying on Uchikawa for the teaching of using benzyl alcohol as a solvent. In fact, Uchikawa discloses benzyl alcohol as part of a long list of general purpose components and one of three potential alcohols (*see*, column 4, lines 7-33, especially lines 9-11 and 31-32 of the Uchikawa patent). Uchikawa also discloses minoxidil as part of this long list of general components, but does not disclose minoxidil anywhere else, much less disclose or suggest any particular formula containing minoxidil (column 4, line 19). In fact, Uchikawa considers including an amine oxide and an anionic surfactant essential to their hair tonic

composition (*see*, column 4, lines 7-9), but does not consider minoxidil essential. As claim 1 indicates, the Uchikawa hair tonic composition requires an amine oxide and an anionic surfactant (*see*, column 11, lines 50-53).

Thus, the combination of teachings of Bazzano, Weiner *et al.* and Uchikawa would produce an encapsulated composition of minoxidil, retinoic acid and amine oxide, wherein the minoxidil was previously made more hydrophilic by either treating with an organic acid, or wherein the minoxidil is encapsulated in cyclodextrin. In no instance would the hypothetical combination produce the claimed invention. As such, Applicants respectfully request that the Examiner withdraw the rejection.

D. Navarro *et al.* (WO 95/25500) in view of Weiner *et al.* (97/12602) and further in view of Uchikawa *et al.*

The Examiner has rejected claims 10-11, 20, and 24 as allegedly being obvious over Navarro *et al.* (WO 95/25500) in view of Weiner *et al.* (97/12602) and further in view of Uchikawa *et al.* In response, Applicants respectfully traverse the rejection.

The Examiner states:[8]

> The references do not teach the use of benzyl alcohol. Uchikawa et al. teaches a hair tonic that contains an active agent such as minoxidil, organic acids such as lactic acid, water, polyhydric alcohols such as glycerin or propylene glycol, and alcohols such as ethanol and benzyl alcohol. Further, the reference teaches a formulation where the alcohol-water mixture is in the instant ratio. (col. 3 and 4, line 45 through line 34). Uchikawa et al teaches the application of the hair composition for the treatment of hair loss. It would have been obvious at the time the invention was made to combine the teachings of Navarro et al, Weiner et al, and Uchikawa and utilize benzyl alcohol in the solvent system. One would have been motivated to do so since Uchikawa et al teach the use of either ethanol or benzyl alcohol as functional equivalents, i.e. solvents, in the hair tonic. Therefore, it is prima facie obvious to substitute one solvent for another, i.e. WO's ethanol with instant benzyl alcohol,

[7] Page 9 of the Office Action dated September 22, 2004.
[8] Page 10 of the Office Action dated September 22, 2004.

since the prior art establishes that both are functionally equivalent and are utilized for the same purpose.

The Examiner is relying on Uchikawa for the teaching of using benzyl alcohol as a solvent. Again, Uchikawa discloses benzyl alcohol as part of a long list of general purpose components and one of three potential alcohols (*see*, column 4, lines 7-33, especially lines 9-11 and 31-32 of the Uchikawa patent). Uchikawa also discloses minoxidil as part of this long list of general components, but does not disclose minoxidil anywhere else, much less disclose or suggest any particular formula containing minoxidil (column 4, line 19). In fact, Uchikawa considers including an amine oxide and an anionic surfactant essential to their hair tonic composition (*see*, column 4, lines 7-9), but does not consider minoxidil essential. As claim 1 indicates, the Uchikawa hair tonic composition requires an amine oxide and an anionic surfactant (*see*, column 11, lines 50-53).

As discussed in detail above, Applicants believe that the combination of Navarro and Weiner *et al.* would eviscerate Navarro's primary aims and render Navarro's invention unsatisfactory for its intended purpose. The proposed modification that the Examiner contemplates of interchanging a "lactic acid salt of minoxidil" as taught by Weiner *et al.* with "γ-cyclodextrin encapsulated minoxidil" would no longer follow the encapsulation teaching of Navarro. In the absence of cyclodextrin, there would be insufficient penetration without the presence of high concentrations of propylene glycol, which tends to give a greasy, shiny and unattractive appearance to the hair. Thus, the Examiner's proposed modification would destroy Navarro's objective of producing a lotion which is pleasant to use by formulating minoxidil within an inclusion complex of cyclodextrin. As such, Applicants respectfully request that the Examiner withdraw the rejection.

E. Di Schiena (U.S. 4,866,067) in view of Weiner *et al.*

The Examiner has rejected claims 1-3, 5-6, 8-9, 12-19, and 21-23 as allegedly obvious over Di Schiena (U.S. 4,866,067) in view of Weiner *et al.* In response, Applicants respectfully traverse the rejection.

The Examiner states:

> Di Schiena discloses a foam composition containing the instant active, water, a lower alcohol, and propylene glycol (9%) in a foam composition (note examples). The foam composition also contains cetyl alcohol and a surfactant. Di Schiena teaches methanol, ethanol, or isopropanol as suitable solvents (col. 2, lines 17-20 and examples. Further, the reference exemplifies a lotion containing the active without the use of a glycol, instant amount of water, ethanol, and active (example b). The examples teach a variety of water to lower alcohol ratios. Di Schiena does not teach the use of lactic or acetic acid. WO teaches a topical composition for minoxidil. WO discloses that making materials more hydrophilic, improves penetration through the hair follicle. Minoxidil is modified by reacting it with an organic acid such as lactic acid. See page 4.

As the Examiner is aware, Applicants can rebut a *prima facie* case of obviousness by presenting comparative test data showing that the claimed invention possesses unexpectedly improved properties or properties that the prior art does not possess. *In re Dillon*, 16 U.S.P.Q. 1897, 1901 (Fed. Cir. 1990). In this regard, the Examiner's attention is respectfully directed to Applicants' response dated July 21, 2003. In that response, Applicants submitted data wherein the Di Schiena formulation of Example 3(e) was compared to the present invention. In the response Applicants stated:

> [a]s set forth in paragraph 14, after mixing the constituent parts of the comparative foam formulation ("see Di Schiena example 3(e) foam, col 3, lines 29-38") the resulting mixture was brown in color (see Exhibit B). The formulation of Di Schiena separated into 2 phases (biphasic) upon standing; the bottom layer was brown and opaque, and the top layer was a dark brown color and clear.

In contrast to the Di Schiena formulation, the inventive formulation of the subject application was a clear and colorless single-phase solution. It was stated that the homogeneous nature of the inventive formulation has several advantages, including foam consistency, longer shelf-life, and most importantly, uniformity of dosing. Uniformity of dosing is an important feature of the inventive formulation as it reduces deleterious side-effects known to accompany an administered dose greater than that prescribed. Additionally, the inventive formulation is stable

over long periods of time and at elevated temperatures. However, under the same conditions, the formulation of Di Schiena develops an *insoluble crystalline precipitate.*

Applicants further stated:

> [a]s is currently taught and claimed, the foam of the present invention breaks with shear, which significantly eases topical application. Paragraphs 23-28 of the Abram declaration demonstrate, the inventive foam is relatively stiff below 30°C, but is easily broken down under mechanical shear above 30°C. This temperature is significant, since, in preferred embodiments, the foam is applied topically to the human skin, which has a temperature above 30°C. Unlike the inventive foam, the Di Schiena foam exhibits minimal deformation under mechanical shear over the whole temperature range. Even at 40°C, the Di Schiena foam persists while the inventive sample ***no longer exists as a foam***. (See Exhibit C of the Abram declaration). As declared in paragraph 29: Based on the findings of this study, it would be expected that the inventive foam system is rapidly destroyed when applied topically at skin temperature (32°C), whereas the comparative example would be expected to persist as a foam following topical application.

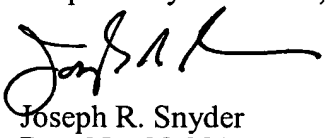
In view of the rejection of the comparative data filed earlier in this application, Applicants have rebutted any obviousness by presenting comparative test data showing that the claimed invention possesses unexpectedly improved properties or properties that the prior art does not possess. *In re Dillon*, 16 U.S.P.Q. 1897, 1901 (Fed. Cir. 1990). Again, the present invention shows unexpectedly improved solution and mechanical properties. In view of the unexpected and surprising results, Applicants submit that Di Schiena does not present a bar under 35 U.S.C. § 103, either alone or in combination, to the patentability of the present application. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

V. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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